INTRODUCTION/BACKGROUND

Prostate cancer is the most common malignancy in men, with an estimated 317,000 cases in 1996 (1). At the time of presentation, an estimated 30% of patients demonstrate overt metastatic disease. A significant proportion of the remaining patients will ultimately relapse after surgery or radiation treatment and develop metastatic disease. Although patients with metastatic disease may be successfully palliated by hormonal therapy, the majority of these patients will ultimately develop progressive disease. Moreover, the effect of hormonal therapy on survival is unknown, and there are no randomized trials which indicate a survival advantage for patients receiving such therapy (2-4). Patients with asymptomatic metastatic disease who have not yet received hormonal therapy represent a population with a small tumor burden in whom progression is inevitable. This group of patients is ideal for evaluation of new therapies, such as immunologic approaches, which may be most effective in a setting of minimal tumor burden.

Since prostate specific antigen (PSA) is normally found only on prostatic epithelial cells and is usually expressed by prostate cancer cells [Wang, 1979], it is an excellent target for immunologic anticancer therapies. The availability of a recombinant vaccinia virus that expresses PSA (constructed by Therion Biologics Corporation in collaboration with the Laboratory of Tumor Immunology and Biology at the NCI) allows clinical evaluation of this concept. Because vaccinia evokes both humoral and cell-mediated immune responses, co-expression of PSA with viral proteins may enhance immunogenicity to PSA, resulting in lysis of cancer cells expressing this protein. Moreover, since vaccinia virus was used for years in vaccinations against smallpox, it has a well-known toxicity and safety profile. Indeed, a similar strategy using a recombinant vaccinia virus expressing carcinoembryonic antigen (CEA) has recently been conducted at the NCI (6,7). At a dose of 1.0×10^7 PFU (plaque forming units), the vaccine was well-tolerated and toxicities consisted only of local cutaneous reactions (6).

A recombinant vaccinia virus expressing human PSA (designated rV-PSA) has been used to immunize rhesus monkeys. There is 94% homology between both the amino acid and nucleic acid sequences of rhesus and human PSA. Immunization of the rhesus monkeys with wild type vaccinia virus (V-Wyeth) or rV-PSA elicited the usual low grade constitutional symptoms of the vaccinia virus infection (8). Otherwise, there was no evidence of any adverse events. A PSA specific IgM response was found in all rV-PSA immunized monkeys. Moreover, one of four monkeys receiving $1X10^7$ PFU rV-PSA and four of four receiving $1X10^8$ PFU rV-PSA developed specific T-cell responses to PSA protein that were maintained for 270 days (8). These studies thus demonstrate the safety and immunogenicity of rV-PSA in a non-human primate and support trials with rV-PSA in man.

This phase I trial currently underway at the Dana-Farber has treated 18 patients. The maximum tolerated dose of rV-PSA is 2.65 X 10^8 PFU given as three vaccinations at 28 day intervals. Local erythema and pustule formation have been grade 1 only. No constitutional symptoms have been seen a follow up period of 9 months. There have been no systemic illnesses or symptoms observed. There has been no evidence of autoimmune signs or symptoms. Three of 18 patients have experienced disease progression with rising PSA values and have gone on to other therapies. Fifteen patients remain clinically stable under close clinical and laboratory observation.

Granulocyte-macrophage colony stimulating factor (GM-CSF) expressing vaccinia virus has been given to patients with metastatic malignant melanoma in phase I trials (11). Flu-like symptoms occurred after 3 of 57 treatment sessions (all patients have intratumoral injections of all dermal / subcutaneous lesions). All patients had partial regression of all injected (and some untreated regional) lesions. No other adverse effects were noted. Several investigators have reported tumor specific immunity in mice with vaccinia virus vectors modified to express GM-CSF (12-14).

GM-CSF expression can produce local injury in autoimmune mice (C3H-1pr, MRL-1pr) but not systemic injury and no injury in non-autoimmune hosts (15). Exacerbation of pre-existing autoimmune thyroiditis has been reported with systemic GM-CSF administration (16). [The exclusion of patients with pre-existing autoimmune diseases have been an eligibility criteria for this study from the beginning]. Since GM-CSF may have additional properties to enhance active specific immunity, we propose to add local subcutaneous injection of GM-CSF to intradermal administration of rV-PSA. There will be consisent close observation of all patients to evaluate for autoimmune or constitutional symptoms. Ten patients will be enrolled who have never received rV-PSA to evaluate toxicity.

We also propose to re-innoculate patients who have previously received rV-PSA. This serves the three study endpoints: to evaluate toxicity in patients with recent vaccinia exposure, to determine if GM-CSF has an effect on cellular and humoral immunity different from rV-PSA alone (patients have prestudy baseline studies), and whether the addition of GM-CSF has enhanced anti-tumor effect compared to rV-PSA alone.

OBJECTIVES

2.1 To assess the toxicity associated with repeated vaccination with recombinant vaccinia virus (rV-PSA).

2.2 To determine the optimal dose of rV-PSA given at monthly intervals based on cellular and humoral immunity.

2.3 To determine whether vaccination with rV-PSA is associated with anti-tumor activity.

2.4 To determine whether GM-CSF has an effect on cellular and humoral immunity different from rV-PSA, and whether the addition of GM-CSF has enhanced anti-tumor effect compared to rV-PSA alone.